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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,899	PETROU ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04/02/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *18,19,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17, 20, 21, 24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/02/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-25 are pending.
Claims 18, 19, 22 and 23 are withdrawn.
Claims 1-17, 20, 21, 24 and 25 are examined on the merits.

This Office Action is in reply to Applicants' correspondence of 4/2/2007. No claim(s) is/are cancelled; claim(s) 18, 19, 22, and 23 is/are withdrawn; claim(s) 24 and 25 has/have been newly added; claim(s) 1, 2, 6, 11, and 21 has/have been amended.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Response to Remarks Concerning Priority

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. However it is noted that basis for the instant claims is not found in the Priority document. For example, claims 1 and 21 include the language of testing for alteration in 'a regulatory region', where the priority document does not support such a specific limitation. Additionally, the claims (i.e. claims 2 and 25) require 'establishing whether the alteration would result in a major disruption to a protein', where there is no such teaching in the priority document. The claims also require elements of Table 3 (i.e. claims 4 and 21) of the instant specification, where the priority document does not present the information contained in Table 3 of the instant specification. As such, the instant claims to not have priority to the filing date of the priority document, and the effective filing date of the instant claims is the filing date of the instant application, 3/23/2004.

Response to Remarks Concerning the Information Disclosure Statement

2. The IDS filed on 04/02/2007 has been considered. It is noted that item 'H' on sheet 2 of 5 has been changed to correct a typographical error in the title of that reference.

Response to Remarks Concerning the Specification

3. The amendment to the specification adding SEQ ID NOs to the listing of primers in Table 1 is accepted, and the Objection to the specification set forth in the previous Office Action is withdrawn in light of the amendment.

Response to Remarks Concerning Sequence Compliance

4. In light of the additions to the Sequence Listing the instant Application is in Compliance with the Sequence Rules as set forth in 37 CFR 1.821-1.825.

Response to Remarks Concerning Claim Objections

5. The Objections to claims set firth in the Previous Office Action are withdrawn in light of the amendments to the claims. With regard to the previous Objections to claims 4 and 21 for the specific recitation of non-elected subject matter (i.e. claims 4 and 21 recite methods requiring the use of SCN1A alterations as presented in Table 3, where in response to the requirement for restriction Applicant has elected for the examination of the claims in so far as they require the c251A→G nucleotide change), the Objection is

withdrawn, but it is again noted that prior to allowance of these claims, the non-elected subject matter will be required to be deleted from the claims.

Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-17, 20, 21, 24 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 5-17, 20, 24, and 25 are unclear over recitation of the phrase 'testing a patient sample for the existence of an alteration in the SCN1A gene', as recited in claim 1, because it is unclear what applicant intends for the phrase to encompass and thus the metes and bounds of the claimed subject matter are not clearly defined. It is unclear to what any patient's SCN1A gene would be compared in order to detect 'an alteration'. For example, many polymorphic and mutant forms of the SCN1A gene are known in the art, thus it is unclear if detecting such a polymorphic or mutant form of the gene in a patient would not be considered 'an alteration' as compared to any of these known forms. Neither the claims nor the specification set forth any standard to which a patient SCN1A gene may be compared to identify 'an alteration'.

Response to Remarks

Applicants have traversed the rejection of claims as indefinite over requirement of identifying in a sample 'an alteration'. Applicants have argued (p.15 of Remarks) that

the specification teaches that the nature of alterations may encompass all forms of gene mutations, and that assay systems that compare a patient sample to 'wild-type SCN1A DNA' for example from 'normal individuals'. This argument has been considered but is not found to be persuasive to overcome the rejection. The rejected claims do not provide any basis for a particular standard sequence that is used for comparison to determine that any analyzed patient SCN1A sequence has 'an alteration'. The Application does not provide any particular sequence, as identified by a SEQ ID NO, that can be used to determine that a patient sample is in any way different. Given the polymorphic nature of the SCN1A gene (where for example the instant specification teaches that the gene contains 'benign polymorphisms' that would be found in 'normal individuals') it is not clear what is required to be detected in order to determine that a patient sample has 'an alteration in the SCN1A gene'.

The rejection as set forth is MAINTAINED.

Claims 1-17, 20, 24 and 25 are unclear over recitation of the phrase 'known to be' in reference to whether a detected alteration is SMEI associated or non-SMEI associated. It is not clear from either the claim or specification what is required, for example, for any particular mutation to be 'known to be SMEI associated'. For example, does an alteration 'known to be associated with SMEI' require that the mutation is associated with SMEI at some particular level of statistical significance, or know by a specific group of researchers to be associated with SMEI, or published in a certain publication as 'associated with SMEI'.

Response to Remarks

Applicants have traversed (p.17 of Remarks) the rejection of claims as indefinite over recitation of the limitation requiring determining that an alteration is 'known to be' SMEI associated of non-SMEI associated. Applicants have argued that p.6 ln22-33 of the instant specification recites 'that the alteration in the SCN1A gene is one that has previously been associated with SMEI', and that p.41 lns.23-33 of the specification teaches that four particular SCN1A mutations 'had previously been associated with SMEI'. Applicants conclude the argument indicating that one of ordinary skill would recognize that when a particular mutation is said to be 'know to be SMEI associated', the mutation has previously been associated with SMEI in the art. This argument is not found to be persuasive. Initially it is noted that the claims have no requirement that 'know to be' associated is in any way related to something previously described in the art. Furthermore, the specification at page 6 does not serve to clarify what is considered 'known to be' SMEI associated, only that there may be some mutations that have previously been associated with SMEI, and page 41 of the specification merely provide four particular mutations that are asserted to have previously been associated with SMEI. These portions of the specification to do not clearly establish what is required of any of the many possible mutations in the SCN1A gene to be, for example, know to be associated with SMEI'.

The rejection as set forth is MAINTAINED.

Claims 2 and 25 are unclear over recitation of the phrase 'a major disruption to the protein', as recited in each of claims 2 and 25, as it is not clear if Applicant intends to claim a method requiring the detection of any particular alteration to the SCN1A gene. Neither the claim nor the specification nor the prior art offer a clear definition of what is considered 'a major disruption'.

Response to Remarks

Applicants have traversed (p.19 of Remarks) the rejection of claims as indefinite over recitation of the phrase 'a major disruption to the protein'. Applicants have argued that the specification at page 42 lines 2-8 teaches 'a major disruption to the protein (such as a truncating alteration)'. The argument has been considered but is not found to be persuasive. It is noted that page 42 of the specification does not provide 'a truncating alteration' as a limiting definition for 'a major disruption to the protein', but merely provides that a truncating alteration is exemplary of a major disruption.

Claim 4 is unclear over recitation of the requirement 'wherein the alteration is one identified in Table 3', where, consonant with the election, Applicant has elected the missense mutation corresponding to the c251A→G nucleotide change. However, the phrase as written in the claim is unclear if the claim requires, for example, detection of a G at a particular position, or detection of a cysteine-encoding codon at a particular position. Because Table 3 includes a variety of information about each alteration, it is not clear what features provided in Table 3 are required to meet the limitations of the claims.

Response to Remarks

Applicants have traversed (p.20 of Remarks) the rejection of claims as indefinite over the requirement that an alteration is 'one identified in Table 3'. Applicants argue that the contention that the subject matter of the claim should be limited to the elected nucleotide change is premature, as non-elected subject matter may be rejoinable. This is not found to be persuasive because at issue is not Table 3 contains non-elected subject matter, but that for any particular specific mutation, a variety of different elements is provided (e.g.: missense, c251A→G, Y84C, SEQ ID Numbers 1, 26). As such it is unclear which of the particular elements is required to establish the particular alteration 'identified in Table 3'.

Claim 21 is unclear over recitation of the phrase 'alteration as laid out in Table 3', where, consonant with the election, Applicant has elected the missense mutation corresponding to the c251A→G nucleotide change. However, the phrase as written in the claim is unclear if the claim requires, for example, detection of a G at a particular position, or detection of a cysteine-encoding codon at a particular position. Because Table 3 includes a variety of information about each alteration, it is not clear what features provided in Table 3 are required to meet the limitations of the claims.

Response to Remarks

Applicants have traversed (p.21 of Remarks) the rejection of claims as indefinite over the requirement that an alteration is 'as laid out in Table 3'. Applicants argue that the contention that the subject matter of the claim should be limited to the elected

nucleotide change is premature, as non-elected subject matter may be rejoinable. This is not found to be persuasive because at issue is not Table 3 contains non-elected subject matter, but that for any particular specific mutation, a variety of different elements is provided (e.g.: missense, c251A→G, Y84C, SEQ ID Numbers 1, 26). As such it is unclear which of the particular elements is required to establish the particular alteration 'as laid out in Table 3'.

Claim 21 is unclear over recitation of the phrase 'known to be' in reference to whether a detected alteration is SMEI associated or non-SMEI associated. It is not clear from either the claim or specification what is required, for example, for any particular mutation to be 'known to be SMEI associated'. For example, does an alteration 'known to be associated with SMEI' require that the mutation is associated with SMEI at some particular level of statistical significance, or know by a specific group of researchers to be associated with SMEI, or published in a certain publication as 'associated with SMEI'.

Response to Remarks

The response to the traversal of the rejection of claims for recitation of the limitation that any alterations is 'known to be', for example, SMEI associated, has been detailed earlier in this Office Action.

New Grounds of Rejection

Claims 1-17, 20, 21, 24, and 25 are unclear over recitation of the purpose of the claimed methods as stated in the preambles of independent claims 1 and 21 as 'a method for determining the likelihood that a patient suspected of having SMEI does or does not have SMEI' because in each of claims 1 and 21, part (3) step (c) concludes with a further analysis to establish whether an alteration is a SMEI associate or non-SMEI associated alteration, but does not require the determination of any likelihood of a patient having SMEI. It is thus unclear how a method concluding with part (3) step (c) accomplishes the purpose of the method as stated in the preamble of the independent claims.

Claim Rejections - 35 USC § 112 1st¶ - Written Description

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-17, 20, 21,24, and 25 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is noted that this rejection of method claims is made over the lack of an adequate written description of the broadly claimed methods encompassing the detection of any alteration in the SCN1A gene in a patient and making a diagnosis by

detecting the alteration. In the instant case, the mutations are a critical element of the claimed method and therefore must be adequately described.

> Applicant is referred to the guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

The claims of the instant application are drawn to methods of diagnosing SMEI in a patient requiring the detection of an alteration in the SCN1A gene. The methods of the claims encompass detecting any alteration in any portion of the SCN1A gene. Claims 4 and 21, consonant with Applicants' Election, are drawn to methods requiring the detection of an alteration in the SCN1A gene identified as 'the missense mutation corresponding to the c251A→G nucleotide change'.

With specific regard to the limitations of claims 4 and 21, which, consonant with Applicants' Election, require the detection of an alteration that is described in Table 3 as a c251A→G nucleotide change, the art with regard to the numbering of nucleotides in the SCN1A gene indicate that there are different numbering systems applicable to the SCN1A gene. First, it is noted that while Table 3 indicates a nucleotide change at position 251 in which a G is substituted for an A and further specifies that this mutation is shown in SEQ ID NO: 1, the altered position with the G content in SEQ ID NO: 1 is at position 517 of SEQ ID NO: 1. Furthermore, within the art of the SCN1A gene sequence, the altered position is at position 269 in GenBank Locus AF2258985 and GenBank Locus NM_006920 (see provided sequences). Thus an adequately specific written description is not provided for a method encompassing the identification of a 'c251A→G' mutation. This portion of the rejection may be overcome by more

specifically identifying the nature of the identified mutation as a G at position 517 of SEQ ID NO: 1, as consonant with the Election.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the detection of an enormous number of alterations in the SCN1A gene. The specification teaches (p.6 ln.9):

> The nature of the alterations in the SCN1A gene may encompass all forms of gene mutations including deletions, insertions, rearrangements and point mutations in the coding and non-coding regions such as the promoter, introns or untranslated regions. Deletions may be of the entire gene or only a portion of the gene whereas point mutations may result in stop codons, frameshifts or amino acid substitutions. Point mutations occurring in the regulatory regions of SCN1A, such as in the promoter, may lead to loss or a decrease of expression of the mRNA or may abolish proper mRNA processing leading to a decrease in mRNA stability or translation efficiency.

Thus the claims encompass methods comprising the detection of any alteration anywhere in the SCN1A gene and further require ascertaining whether the alteration is 'known to be SMEI associated or non-SMEI associated'. However, the specification does not teach methods comprising the detection and analysis of nucleic acid sequences comprising SCN1A alterations of such a large genus as encompassed by the claims.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The specification provides only methods comprising the detection and analysis of the 30 specific mutations of Table 3, and an SCN1A sequence that contains each particular mutation in SEQ ID NO: 1-25, and 49-53. The instant specification does not teach any methods

comprising the analysis of any other particular alterations in the SCN1A gene. The specification further provides (Table 3, footnote 4) that a c677C→T mutation was found in a patient diagnosed with SMEI, and also seen in an individual that was not clinically diagnosed with SMEI.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other than nucleotide sequence or position within a particular gene), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, while the specification asserts one may make a diagnosis of 'high probability of SMEI' or 'low probability of SMEI' by ascertaining that a detected mutation is 'SMEI associated' or 'non-SMEI-associated', respectively, the specification actually provides methods comprising only the detection of the 30 mutations disclosed in Table 3, and does not provide any teachings regarding what is required, for example, for any of the multitude of particular mutations encompassed by the breadth of the claim to be 'SMEI associated'. As demonstrated by the example of the c677C→T mutation, if a mutation is found in a SMEI patient and also in a patient not clinically diagnosed with SMEI, is such a mutation considered 'SMEI associated' or 'non-SMEI-associated'? Thus the teachings of the specification do not provide guidance as to how one would a priori identify an SCN1A mutation that is 'known to be SMEI associated or non-SMEI associated'.

Applicants' attention is directed to the decision in In re Shokal, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

The specification of the instant application discloses methods comprising the detection of the several particular alterations in the SCN1A gene of patients know to be either SMEI-diagnosed or non-SMEI-diagnosed. However the disclosure of the particular methods does not constitute an adequate written description of the broadly claimed methods which require diagnosing SMEI based upon, for example, determining whether the detected alteration is 'known to be SMEI associated or non-SMEI associated' because the specification does not clearly establish, given the multitude of nucleic acid sequences encompassed by the claims, what is required for any particular alteration to be 'known to be SMEI associated or non-SMEI associated'. Similarly, given the numerous nucleic acid sequences that are considered the 'SCN1A gene' as encompassed by the claimed methods, the specification does not provide a description of what is required for the detection of any 'alteration' in the SCN1A gene. Thus one of skill in the art cannot envision the detailed chemical structure of the sequences encompassed by the claimed methods, regardless of the complexity or simplicity

of the method of detection. Adequate written description requires more than a statement that methods comprising the detection of sequence variants or 'alterations' within a particular region of a genome or with some particular association (e.g. 'known to be SMEI associated) are part of the invention and reference to a potential method for their identification. The particular nucleic acid sequences are themselves required.

In conclusion, the limited information provided regarding particular mutations as provided in the instant specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of the broadly claimed nucleic acids encompassed by the claimed methods. Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Response to Remarks

Applicants have traversed the rejection of claims for lack of adequate written description. Applicants' remarks (p.24 of Remarks) point to pages 12 through 14 of the specification which discusses general methodologies for the analysis of nucleic acids and proteins. The cited portion of the specification does not serve to particularly and specifically describe such a breadth of mutations as encompassed by the claims either by specific structure (i.e. nucleotide sequence) or characteristic description (e.g. such that any skilled artisan might recognize the required mutation). In fact the portion of the specification cited in the

Remarks (p.25 of Remarks, lines 10-14) indicates that Applicants are in possession of a limited number of particular mutations (as identified by specific sequences) that are indicative of SMEI. Furthermore, the cited portion of the specification does not provide any particular nucleotide sequence that is used as a standard of comparison in any determination of the presence of 'an alteration' in a SCN1A gene of a patient. Furthermore, applicants point to the teachings of page 6 of the specification, which provides that 'severe changes to the SCN1A protein' increase the likelihood that a patient has SMEI and that a mutation may have 'previously been associated with SMEI', as adequate teaching to one of ordinary skill in the art of how to identify a mutation 'known to be SMEI-associated' or 'non-SMEI associated'. However, while page 6 of the specification may serve to indicate some particular (i.e. the mutations of page 41 of the specification as cited on page 26 of the Remarks) SCN1A mutations that have met some particular criteria (i.e. published in a journal article) such that Applicant considers the mutations 'known to be SMEI associated, such a teaching does not adequately describe the breadth of the nucleic acid mutations encompassed by the claims. Finally, while Applicants assert (p.26 of Remarks) that one of ordinary skill in the art would ascertain that a particular mutation is 'known t be SMEI associated' if the particular mutation has been previously associated with SMEI in the literature, the requirement of any particular literary reference, or any other criteria, is not in fact set forth in the specification or a required limitation of the rejected claims.

With regard to the rejection of claim requiring identification of an alteration that is 'c251A→G', as consonant with the election, Applicants have not provided any arguments as to how the required 'c251A→G' is adequately described in the specification such that the skilled artisan would be aware of the particularly required nucleic acid mutation (in light of the fact that the art with regard to the numbering of nucleotides in the SCN1A gene indicate that there are different numbering systems applicable to the SCN1A gene, as discussed in the rejection).

The rejection, as set forth, is MAINTAINED.

Claim Rejections - 35 USC § 112 1st¶ - Enablement

10. Claims 1-17, 20, 21, 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The claims of the instant application are drawn to methods for the diagnosis of SMEI in a patient.

The claims encompass the detection of any alteration anywhere in the SCN1A gene of a patient and making a diagnosis if the detected mutation is known to be SMEI associated or non-SMEI associated.

Claims 4 and 21, consonant with the Election, are drawn to the detection of the nucleotide change c251A→G.

The claims further encompass the diagnosis of a low probability of SMEI if the detected alteration is an inherited mutation, and a diagnosis of a high probability of SMEI if the detected alteration is a de novo mutation in the patient.

The claims encompass any subject organism, including any non-human subjects.

The claims thus require knowledge of whether or not any particular detected mutation is know to be SMEI associated or non-SMEI associated, and further depend on the concept that any detected de novo mutation in the SCNA1 gene is indicative of SMEI.

Direction provided by the specification and working example

The instant specification teaches the sequence analysis of the SCN1A gene in a study population of individuals that had been diagnosed with SMEI from a clinical analysis or had severe encephalopathies occurring during the first 12 months of life (Example 1, p.38 lns.1-5). The specification teaches the results of analysis of the 26 exons of the SCN1A gene in a total of 96 patients with the clinical epilepsy phenotype of the patients being hidden during the analysis. The specification further teaches that of the 96 patient samples analyzed, 34 samples were shown to have an alteration in the SCN1A gene, and of those 34 samples, 28 samples were from patients with a clear SMEI phenotype based on a clinical analysis (p.41 lns.24-36).

The specification uses the above data from the example to draw the conclusion that 'if an SCN1A alteration is found in a patient, then the patient has an 82% chance (28/34) of having SMEI. However, this conclusion is based only on the analysis of encephalopathic patients. There is no analysis of any general population to indicate that SCNA1 alterations of any kind in any portion of the gene (as is encompassed by the scope of the claims) occur with any particular frequency.

The specification provides no analysis of the SCN1A gene in any non-encephalopathic controls.

The specification provides no analysis of any non-human patients.

Insofar as the claims may encompass the analysis of the SCN1A protein for the detection alterations in the SCN1A gene, it is relevant to point out that the specification provides no examples of any methods in which the SCN1A protein is analyzed. The specification indicates that immunoassays for the SCN1A gene product are not currently known (p.12 lns.11-12).

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the detection of an alteration in any particular known gene sequence is high, the unpredictability of drawing an association between any gene mutation and a particular phenotype for diagnostic purposes is even higher. The unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The unpredictability with regard to ascertaining whether a mutation is 'known to be SMEI associated' is demonstrated by the instant specification. For example, Table 3 of the specification indicates that a c677C→T mutation was found in a patient diagnosed with SMEI, and also seen in an individual that was not clinically diagnosed with SMEI. Thus it is unpredictable as to what would be required for any particular mutation to be considered 'known to be SMEI associated'. It is not predictable if one of skill in the art would consider finding a particular mutation in one particular patient with SMEI evidence that the mutation is 'known to be SMEI associated'. With particular regard to the elected nucleotide change c251A→G, is the finding of this mutation in one SMEI patient in an encephalopathic population sufficient to indicate that this mutation is 'known to be SMEI associated'. The post filing art of Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph).

Furthermore, with regard to the diagnosis of a patient based on a establishing whether and identified mutation is an inherited or de novo mutation, the specification does not provide any analysis to indicate a significant association between, for example, the presence of a de novo mutation and the SMEI phenotype. GeneCard output

indicates that there are 345 polymorphic variants of the SCN1A gene (GeneCard output page 6), thus it is clear that there are a multitude of alterations in the SCN1A gene (e.g. silent mutations, mutations in introns, missense mutations that do not effect the function of the encoded protein) that, even if they are de novo (i.e. not inherited from a parent), would not be indicative of a diagnosis of SMEI in a patient. Similarly, the art of Fukuma et al (2004) teaches the identification seven mutations in the SCN1A gene that are present in SMEB patients (Table 1), which is a diagnosis distinct from SMEI (p.141 – Patients). This fact is also demonstrated by the data of Table 3 the instant specification, which provides five SCN1A gene mutations, including 2 truncation mutations, that are not associated with SMEI. Additionally, the specification provides no data regarding the de novo detection of SCN1A alterations in a non-encephalopathic population. The prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant (Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion). It is thus unpredictable as to whether or not one can reliably diagnose a patient as having SMEI merely by identification of a de novo mutation. This is exemplified by the post-filing art of Kimura et al (2005), which teaches the presence of an SCN1A mutation in two related SMEI patients where the mutation was inherited from their father (Fig 1).

It is further relevant to point out that the example of the instant specification analyzes only an encephalopathic population, and does not provide any control

population of random selected individuals. This is particularly relevant considering the teachings of Mulley et al (as cited in the IDS) which indicates that a significant number of SMEI cases have a family history of GEFS+ (p.173 – SCN1A mutations in SMEI). The reference further suggests that GEFS+ genes may interact with modifier genes elsewhere in the genome to account for cases of SMEI diagnosed in families with GEFS+. It is thus unpredictable as to whether or not finding any particular specific mutation in one SMEI patient would thus make that mutation 'known to be associated with SMEI', and whether or not finding the mutation in any individual would in fact be indicative of a diagnosis of SMEI.

Regarding the required limitations of claim 11, it is not predictably established by either the instant specification or the prior art that detecting a length difference in an SCN1A exon amplified from a patient sample as compared to a wild-type SCN1 A gene is specifically indicative of a truncation mutation. The specification indicates (p.6 lns. 24-25) that truncation mutations are those mutations such as frameshift mutations and nonsense mutations that lead to a truncated protein by creating an mRNA the translation of which is terminated prior to that of the non-mutated gene transcript . However, the art of Fukuma et al (2004) teaches that there are SCN1A mutations which would alter the size of the amplified exon, but not result in a truncation mutation and not be found in an SMEI patient (for example the F1756del mutation indicated in Table 1 and Fig 2C).

Additionally it is noted that the art of Sugawara et al (2003) teaches that SMEI associated mutations in the SCN1A gene result in functional differences in the encoded

protein. However, even given the know structure of the SCN1A protein, neither the art nor the teachings of the instant specification teach how one may a priori identify a mutation in the SCN1A gene that is associated with SMEI or will effect the functionality of the resulting protein. Such unpredictability is demonstrated by the instant specification, where in Table 3, several mutations, including truncating mutations, are indicated as non-SMEI associated.

Insofar as the claims may encompass the analysis of the SCN1A protein for the detection alterations in the SCN1A gene, it is relevant to point out that while the specification contemplates the development of mutant specific antibodies, the specification provides no examples of the detection of particular amino acid content in a polypeptide. The specification does not teach that it is in fact possible to differentiate between, for example, a tyrosine and a cysteine at amino acid 84 of SEQ ID NO: 26 (as consonant with the Election), or any particular SCN1A mutation, using a particular antibody, nor does the specification teach any particular antibody that is specific for this mutation. It is unpredictable whether any particular mutant form of the SCN1A protein would be sufficient to result in the production of antibodies that can differentiate between different molecules. In some cases, an antibody elicited by one antigen can cross-react with a different antigen if the two different antigens share an identical or very similar epitope (Goldsby et al., 2003, p. 141). Furthermore, the art teaches the unpredictability with regard to using an antibody to analyze a protein at the single amino acid level of specificity. DePalma teaches that, in contrast to gene hybridization techniques, antibody-protein interactions vary greatly and suffer from unpredictable

cross-reactivity, and that antibodies are difficult to make (page 4, third full paragraph). It is thus unpredictable as to whether or not methods based on the analysis of the SCN1A protein would be suitable for the detection of particular mutations in the SCN1A gene.

Given the lack of data in the specification or the art regarding the effect of mutations in the SCN1A gene of non-human subjects on the diagnosis of the SMEI phenotype, it is unpredictable as to how one might extrapolate the data of the instant specification to any non-human animal.

Quantity of experimentation required

A large amount of experimentation would be required to make and use the claimed invention. In order to use the claimed method one would have to determine that any detected alteration is 'known to be SMEI associated or non-SMEI associated'. However the specification provides no guidance as to what is required to ascertain whether any detected alteration is, for example, 'know to be SMEI associated'. Given, for example, the data presented in the instant specification, where a mutation is found in an SMEI patient as well as a non-SMEI patient, one would have to establish that any mutation is in fact 'SMEI associated'. Furthermore, regarding establishing a diagnosis of SMEI based on the presence of an alteration not known to be either SMEI associated or non-SMEI associated where the mutation is a de novo mutation, given the extremely large number of alterations to the gene encompassed by the claims, one would have to establish that in fact any newly identified de novo mutation is associated with SMEI in a significant fashion, and thus indicative of a particular diagnosis.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance of the specification and the specific working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention.

Response to Remarks

Applicants have traversed the rejection of claims for lack of enablement. Applicants traversal (pages 27-31 of Remarks) details the various steps of the claimed methods and how applicant proposes to use the claimed methods, but the traversal does not address the issues of enablement as detailed in the rejection.

Applicants arguments that 'most cases can be diagnosed by looking at the totality of the genetic landscape for SCN1A' (p.29 lns.8-9 of Remarks) and that 'any and all mutations in the SCN1A subunit fall into one of these three categories' (i.e. the categories of 'known to be SMEI associated', 'known not to be SMEI associated', and 'previously unknown') (bottom of page 31 of Remarks) in fact speak to the enablement rejection as set forth in the Office Action. Applicant has supplied a circular argument that, for example, diagnosis of SMEI is made by identifying an alteration that is known to be associated with a diagnosis of SMEI. As such it appears that Applicants invention required the particular knowledge of any and every mutation that is in fact associated with

SMEI. Additionally Applicants claimed methods are based on the notion that any identified *de novo* alteration of the SCN1A gene is indicative of SMEI, where the data presented in the specification (see footnote 4 of Table 3) indicates that various mutations are not associated with SMEI, though there is simply no indication as to how one might in fact reliably predict that any newly discovered mutation, within the large breadth of the claims, is in fact indicative of an increased likelihood of SMEI. And while applicants assert (p.30 of Remarks) that 'a great number of mutations associated with SMEI occur in the SCN1A gene', it is noted that Table 3 of the instant specification present 30 mutations of the SCN1A gene where the SCN1A mRNA contains over 8000 bases of sequence. As such, the breadth of the claimed subject matter is well beyond the particular teachings of the instant specification.

The rejection as set forth is MAINTAINED.

New Ground of Rejection
Claim Rejections - 35 USC § 103 - Obviousness

The Examiner has rejected the claims of the instant application for a lack of enablement under 35 USC 112 1st¶. The claims are also rejected under 35 USC 103 as obvious in view of the cited reference (Claes et al, 2001). It is noted that the applied reference provides the same data as the instant specification, thus if the Applicant considers the instant specification enabling for the claims, the applied reference is similarly enabled for the particular subject matter taught in the reference. However, as detailed in the rejection of claims under 35 USC 112 1st¶, the rejection of claims for lack of enablement is based in part on the enormous breadth of the claims in determining the likelihood that a patient has SMEI by the identification of any alteration in the SCN1A

gene. In as much as the claims encompass methods of SMEI diagnosis by identification of any alteration that is 'known to be SMEI associated', the claims encompass a diagnosis of a high probability of SMEI upon identification of the specific alterations disclosed in Claes et al.

Thus, for example, in view of the teachings of Claes et al it would be obvious for the skilled artisan to perform a method in which the SCN1A gene of a patient is sequenced (relevant to step 1 of claim 1) and identification of the c.664C→T mutation (as disclosed in Table 2 of Claes et al as being a mutation in an SMEI patient) as an alteration 'known to be associated with SMEI' results in a diagnosis of a high probability of SMEI (relevant to step 3 part a of claim 1). Such a method would satisfy the limitations of claim 1.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-3, 5-10, 12, 16, and 20, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Claes et al (2001).

Claes et al teaches the analysis of mutations in the SCN1A gene and the relation of the mutations to SMEI.

Regarding claim 1, Claes et al teaches testing a patient sample for the existence of an alteration in the SCN1A gene (Table 2), as required by step (1), and identifying the nature of the mutation as required by step (2) part (b). Given that the mutations were first described by the work presented in the reference, relevant to step (3)(a), the reference establishes that the particular mutations are associated with SMEI.

Regarding claims 2 and 3, Claes et al teaches the identification of frameshift mutations that create premature stop codons (Table 2), which is establishing that the detected alteration is a truncation mutation that would result in a major disruption to the protein.

Regarding claims 5 and 6, Claes et al teaches performing an assay to detect a mutation (DHPLC), and further analysis to determine the nature of the mutation (sequence analysis) (p.1328 – Mutation detection and molecular-genetic analysis).

Regarding claims 7, 9, 10, 16 and 20, the reference teaches the analysis of SCN1A mutations using DHPLC and BigDye terminator-based sequencing, which are assays that encompass DNA hybridization (relevant to claim 7), high performance liquid chromatography (relevant to claim 9), electrophoresis (relevant to claim 10), the use of enzymes (relevant to claim 16), and DNA sequencing (relevant to claim 20).

Regarding claims 8 and 12, the reference teaches the amplification of genomic DNA from patients using oligonucleotide primers (Table 1), where such primers are SCN1A gene probes and oligonucleotides, and because of the specific nature of an DNA:DNA hybridization, such primers are allele specific probes at least insofar as they specifically hybridize to nucleic acid containing the sequence of a cognate primer binding site.

Regarding claims 24 and 25, the reference teaches determining whether mutations were present in either of the unaffected parents (thus considering genetic data for parents, relevant to step (a) of claim 24), and determining that a mutation was absent from the parents (thus establishing that the mutation has arisen de novo)

(p.1329, right col., last ¶). Relevant to claim 25, the reference teaches that *de novo* mutations are probably a major cause of SMEI.

While Claes et al teaches the analysis of the SCN1A gene in patients, Claes et al does not *per se* perform a method of determining the likelihood that a patient suspected of having SMEI does have SMEI. However, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the explicit teachings of Claes et al to perform an analysis of a patient suspected of SMEI that meets all of the required limitations of the rejected claims. Given the teachings of Claes et al it would be obvious to analyze the SCN1A gene of a patient where upon the identification of any of the mutations of Table 2 of Claes et al, the skilled artisan would recognize such a mutation as an alteration 'known to be associated with SMEI' and provide a determination that there is a high probability that such a patient has SMEI. In view of the teaching of Claes et al, it would further be obvious to use the particular techniques of Claes et al because Claes et al teaches the successful analysis of the SCN1A gene in SMEI patients using those particular techniques. On would be motivated to perform a diagnostic assay on a patient using the techniques and teachings of Claes et al based on the teaching of Claes et al that particular mutations in the SCN1A gene are indicative of SMEI (p.1330 –Discussion) where the skilled artisan would recognize the diagnostic properties of identifying such a mutation in a patient.

Response to Remarks

Applicants have traversed the previous rejection of claims under 35 USC 102 as anticipated by the teachings of Cleas et al. Applicants arguments (p.33-35 of Remarks)

in light of the amendments to the claims have been considered and the rejection as previously set forth is WITHDRAWN.

A new rejection of claims under 35 USC 103 as obvious in view of the teachings of Cleas et al has been set forth. As set forth in the rejection, a diagnostic method in which the particular alterations described by Claes et al are identified in a patient and used to render a diagnosis of a high probability of SMEI. And while the rejected claimed methods are generically and broadly drawn to the identification of any SCN1A alteration, it is noted that a method in which a particular mutation is identified and used to diagnose SMEI will satisfy the limitations of the claimed methods (see MPEP 2131.02 for analysis of 'Genus-Species Situations').

13. Claims 11, 13-15, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Claes et al (2001) in view of Wong et al (2001, US Patent 6,331,614).

The teachings of Claes et al are applied to claims 11, 13-15, and 17 as they were previously applied to claims 1-3, 5-10, 12, 16, and 20, 24 and 25.

Claes et al does not specifically teach methods detecting alterations in gene sequences including the required limitations of the rejected claims.

Wong et al teaches a variety of methods for the analysis of alterations in gene sequences.

Regarding claim 11, Wong et al teaches methods in which alteration in a gene sequence is detected by determining the size of an amplification product, where a faster migrating sample is indicative of an alteration (col.42 lns.25-37).

Regarding claims 13, 14, and 15, Wong et al teaches that various methods assay may be used to test for the existence of an alteration in a gene sequence, including SSCP (e.g. col37 ln.39) relevant to claim 13, RNase protection (e.g. col.5 ln.28) relevant to claim 14, and DGGE (e.g. col.6 ln.41). Regarding claim 17, Wong further teaches assay methods comprising the use of mutS (e.g. col.7 ln.8).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used any assay technique know in the art for the detection of the SCN1A alterations associated with SMEI as taught by Claes et al. One would have been motivated to use any additional techniques, including the assay methods taught by Wong et al, to have alternative methods for alteration detection comprising the use of different available reagents.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 103 as obvious over the teachings of Claes et al and Wong et al. Applicants argue (p.36 of Remarks) that Claes et al fails to teach methods of detecting alterations in gene sequences including elements of the present claims. It is noted that a new rejection of the amended claims under 35 USC 103 as obvious in view of the teachings of Claes et al (as detailed above) has been set forth in this Office Action. As such the Examiner has addressed the argument that Claes et al does not teach the required limitations of the rejected claims.

The Rejection as set forth is MAINTAINED.

Conclusion

14. No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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